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(54) PRODUCTION OF SPONGE

(57) Abstract:

PURPOSE: To produce a sponge which has a uniform number of holes and an even hole size and is useful to a medical sponge-like porous base material, by drying by freezing an emulsion produced as a result of a volite organic solvent being added to a water phase containing a high molecular substance.

CONSTITUTION: A water phase is produced by dissolving or gelling in water a high molecular substance, an emulsifier, or other component such as a multivalent alcohol if necessary. An oil phase is produced by dissolving a volite organic solvent and together with a component such as medical substances if necessary. The oil phase is then added to the water phase to prepare an O/W type emulsion which transmutes the water phase into a dispersant and the oil phase into a dispersoid. The O/W type emulsion so obtained is dried by freezing, a desired sponge being produced by perfectly volatizing aforesaid solvent thereupon. A natural high molecule such as gum arabic, a semisynthetic high molecule such as methyl cellulose, and synthetic high molecule such as polyvinyl alcohol can be recommended to be used as the high molecule.

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(54) Method of manufacturing a sponge

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Specification

1. Title of the invention

Method of manufacturing a sponge

2. Claims

1. A method of manufacturing a sponge characterised in that an oily phase whose chief constituent is a volatile organic solvent is added to an aqueous phase obtained by adding to water a polymer substance that is water-soluble or forms a gel in water, to prepare an O/W type emulsion of which said aqueous phase is employed as the dispersion medium and said oily phase is the dispersed phase, this emulsion is then freeze-dried and said volatile organic solvent is evaporated.

2. The method of manufacturing a sponge according to claim 1 wherein the ratio of volatile organic solvent with respect to the aqueous phase is 1 to 100 volume%.

3. Detailed description of the invention

The present invention relates to a method of manufacturing a sponge of polymer material that is water-soluble or forms a gel in water, in particular, a spongiform porous base material for pharmaceutical use.

As vehicles such as styptic agents or medicines for the oral cavity, there are previously known formulations constituted by polymers such as gelatine, sodium carboxymethylcellulose in the form of a spongiform film (Published Japanese Patent Numbers S44-22829, 45-28390, 45-40912, 37-3746, 39-639, 35-16496, 45-41111, 50-16407, 40-9431 and 49-46898); as a method of manufacturing these spongiform-based agents, there may be employed the method of freeze-drying a vigorously stirred polymer aqueous solution, or a method of adding the polymer aqueous solution to an activating agent and stirring, followed by freeze-drying.

However, in all of the conventional methods of manufacturing a spongiform vehicle of this type, bubbles of gas are entrained into the aqueous solution of the polymer and the spongiform condition is produced by freeze-drying this; consequently, the amount of these gas bubbles is difficult to control, with the result that the drug is not uniformly dispersed and the inconvenience results that a fixed drug concentration is not achieved. Also, it is difficult to ensure that these bubbles are entrained uniformly and with uniform size into all locations. Consequently, the number of sponge pores formed shows considerable variation depending on location and the pore diameter is also non-uniform. This makes it difficult to obtain a uniformly fine spongiform film, and the quality of the spongiform film is not fixed. Consequently, various problems arise regarding for example adhesion and residence time etc in use of the film. Furthermore, since because of this, control of the bubbles is extremely difficult, it is difficult to obtain a spongiform film of the required properties having the desired number of pores and pore diameter etc. In addition, when freeze-drying is performed, the polymer fibres become aligned in a fixed direction, so drawbacks arise such as that streaks in a fixed direction appear in the spongiform film.

As a result of meticulous investigation aimed at solving the drawbacks of the conventional method of manufacturing a spongiform film described above, the present inventors discovered that a solution or gel could be obtained by addition to water of a polymer substance that dissolves or forms a gel in water

and an O/W type emulsion could be prepared by addition of a volatile organic solvent thereto; and then, by freeze-drying this and evaporating the organic solvent, a sponge with a uniform number of pores and pore diameter over the entire sponge could always be obtained with a fixed quality in a simple fashion. And, if a drug was blended therewith to enable use of this sponge as a vehicle for the drug the concentration of the drug could be kept constant and stable blending of such drugs could be achieved, and moreover, if this was employed as an adhesive bandage for a drug, adhesion and residence properties were excellent and this was also advantageous in regard to absorption of drugs; and thereby arrived at the present invention.

In more detail, the present invention provides a method of manufacturing a sponge characterised in that an oily phase whose chief constituent is a volatile organic solvent is added to an aqueous phase obtained by adding to water a polymer substance that is water-soluble or forms a gel in water, to prepare an O/W type emulsion of which the aqueous phase is employed as the dispersion medium and the oily phase is the dispersed phase, this emulsion is then freeze-dried and the volatile organic solvent is evaporated.

The present invention is described in detail below.

As the polymer substance that is employed in the present invention, any polymer substance may be employed so long as it is water-soluble or capable of forming a gel with water, and is capable of forming a film; however, with the object of being employed as an adhesive bandage for a drug, preferably the polymer substance shows tacky adhesion. As such polymers, natural polymers, semi-synthetic polymers, or synthetic polymers may be used without distinction. As natural polymers, there may be employed for example gum arabic, tragacanth gum, locust bean gum, guar gum, agar-agar, carrageenan, sodium alginate, dextrin, dextran, gelatine, or amylose: as semi-synthetic polymers, there may be chiefly employed cellulose-based polymers; water-soluble cellulose ethers, such as for example methyl cellulose, ethyl cellulose, hydroxylated alkyl cellulose ethers, alkali metal carboxymethylcellulose, or alkali metal cellulose sulphates may be employed. Also, as synthetic polymers, there may be employed for example: water-soluble copolymers of hydrophilic polyvinyl compounds, such as for example polyvinyl pyrrolidone or vinyl pyrrolidone with ethyl acrylate, styrene, vinyl acetate, or other monomer capable of copolymerisation therewith; copolymers of polyvinyl alcohol, partially hydrolysed polyvinyl acetate or vinyl acetate and monomers capable of copolymerisation therewith such as for example acrylic acid, methacrylic acid, crotonic acid, or esters of these; copolymers of allyl acetate, methyl vinyl ether and maleic anhydride; copolymers of polyvinyl sulphonate such as for example polyvinyl sulphonic acid or poly-itaconic acid or polyvinyl carboxyamide such

as for example polyacrylamide or styrene and maleic anhydride; copolymers of ethylene and maleic anhydride; and copolymers of acrylamide and acrylic acid. These polymers may be employed on their own or in the form o f a mixture of two or more such polymers.

According to the present invention, the product of dissolving this polymer in water or converting it to a gel is used as the aqueous phase to form an O/W type emulsion: in this case, an ordinary emulsifier is blended in the aqueous phase. As the emulsifier, any emulsifier may be employed that can be used to form an O/W type emulsion, and anionic, cationic, amphoteric, or non-ionic emulsifiers may be used without distinction. However, since such active agents remain in the manufactured sponge, it is preferable to employ emulsifiers of low toxicity, and, with this in view, non-ionic active agents, which are superior from the point of view of toxicity and mucosal irritation, are suitably employed.

As such non-ionic active agents, there may be employed one or two or more of for example: polyoxyethylene sorbitane fatty acid esters, polyoxyethylene sorbitol fatty acid esters, polyoxyethylene fatty acid esters, polyoxyethylene high alcohol ethers, polyoxyethylene alkyl allyl ethers, polyoxyethylene lanolin derivatives, polyoxyethylene castor oil derivatives, polyoxypropylene, polyoxyethylene cetyl alcohol ether, polyoxyethylene-polyoxypropylene block polymer (pluronic type activating agents) obtained by using polypropylene glycol obtained by polymerisation of propylene oxide as a base and adding ethylene oxide thereto, or cane sugar fatty acid esters. Also, if the cationic activating agent is employed as the activating agent, since cationic activating agents act as sterilising agents, when the sponge obtained is employed in drug applications, this provides a convenient vehicle in respect of certain types of disease. These activating agents may be used by mixing by the method that is normally employed.

Also, if required, a polyhydric alcohol or the like may be blended with the aqueous phase in order to improve the physical properties of the sponge.

In the present invention, as the organic solvent that is employed in order to form the oily phase of the O/W type emulsion, any organic solvent may be employed so long as it is volatile. However, preferably an organic solvent is employed whose specific gravity is close to 1. In this way, a more stable O/W type emulsion can be formed. As such volatile solvents, there may be employed one, or a mixture of two or more, of solvents such as trichloroethane, benzene, cyclohexane, chloroform, n-hexane, ethyl ether, ethyl isobutyl ether, or heptane. It should be noted that these organic solvents are evaporated during the process of manufacture of the sponge, to be described, and scarcely any content thereof, or not at all, is left in the sponge that is manufactured.

Also, preferably the ratio of the volatile organic solvent with respect to the aqueous phase is 1 to 100 volume%; in this way, a sponge can be formed that is excellent from the point of view of drug absorption, in drug applications.

It should be noted that, when the sponge according to the present invention is employed in drug applications, a prescribed drug may be blended beforehand therewith by adding to the aforementioned constituents. In order to achieve this, if the drug is water-soluble, it may be blended with the aqueous phase; if the drug is oil-soluble, it may be blended by dissolving in the volatile organic solvent that is employed.

Next, the method of manufacturing a sponge of the aforesaid polymer using the constituents described above will be described. First of all, the constituents such as the polymer, emulsifier and, if necessary, polyhydric alcohol are dissolved beforehand in water or a gel is formed with water, to create an aqueous phase. At the same time, an oily phase is created by dissolving the constituents such as the drug, if required, in the volatile organic solvent. Next, an O/W type emulsion is prepared in which the oily phase is the dispersed phase and the aqueous phase is the dispersion medium, by adding the oily phase to the aqueous phase. The O/W type emulsion obtained is freeze-dried, and the organic solvent is thereby entirely evaporated. In this way, the target sponge is obtained.

The sponge that is thus manufactured may be employed in various applications such as employment as the vehicle for a drug, for example the base of a dermatologic agent, such as a styptic agent, or the base of an adhesive bandage for body cavities applied for example to the mucosa or teeth, such as within the oral cavity, nasal passages, or female urethra.

When this sponge is employed as a drug vehicle in locations where body fluids are present, such as for example in the oral cavity, it sticks onto the prescribed location. In this way, it manifests tacky adhesive properties by permeation of body fluids into the sponge whose chief constituent is the polymer described above, and the vehicle shows excellent adhesion to this location, with the result that the drug in the vehicle can perform its action. In this case, when employed as an adhesive bandage for a body cavity for purposes of treatment of pyorrhea alveolaris, gingivitis, pericoronitis of wisdom teeth, stomatitis, or cheilitis etc, or application of fluorine in respect of the teeth by blending the required drug with the sponge, as shown in the drawings, preferably the adhesive bandage 1 for the body cavity is employed by a suitable method such as for example application of a film-forming substance in liquid form obtained by dissolving a water-insoluble or poorly-soluble polymer in a suitable volatile solvent to one face of a spongiform film 2 obtained by forming

the aforementioned sponge in the shape of the sheet, or in a mode in which for example a water-insoluble or poorly-soluble spongiform film of mucus-impermeable polymer support layer 3 is formed. In this way, for example when applied to a lesion of the oral mucosa, when the spongiform film 2 is stuck onto this lesion, mucus (saliva) in the oral cavity permeates into the spongiform film 2, causing the polymer that is water-soluble or that forms a gel in water that constitutes this spongiform film 2 to interact with the saliva, manifesting tacky adhesion which causes it to adhere to the lesion, so that the spongiform film 2 of the adhesive bandage 1 is protected by a water-insoluble or poorly-soluble support layer 3. In this way, excellent residence properties are achieved. As a result, there is no possibility of the spongiform film 2 being easily dispersed and the spongiform film adheres to the lesion in a stable fashion over a long period. Furthermore, it cannot perform tacky adhesion with other sites, thereby making it possible to improve usability and the feeling during use. In this case, if the support layer 3 is mucus-impermeable, the persistence of the drug is improved; if the support layer 3 is mucus-permeable, rapid action of the drug is improved.

Thus, since, with the method manufacturing a sponge according to the present invention, an O/W type emulsion is prepared by adding an oily phase whose chief constituent is a volatile organic solvent to an aqueous phase obtained by dissolving or converting to a gel in water a polymer that is water-soluble or that forms a gel in water, freeze-drying this O/W type emulsion and evaporating the aforesaid volatile organic solvent, the properties of this O/W type emulsion, such as the volume ratio of the oily phase of the aforesaid emulsion and the particle size of the oily phase particles can be adjusted in a simple manner and by suitably controlling the properties of the emulsion in this way a sponge can be manufactured in a simple manner that is of uniform pore size and pore diameter over the entire sponge and sponges of fixed quality can be reliably manufactured having the desired required properties in regard to pore diameter and pore size etc. For example, a uniform fine sponge can be reliably obtained in a simple fashion by making the particle size of the emulsion small and forming a large number of particles; contrariwise, a coarse sponge can be obtained by making the particle size large. Furthermore, with the method according to the present invention, if a drug is blended therewith in order to make it possible to employ the sponge obtained as a drug vehicle, by making the added amount of organic solvent constant, since the drug is uniformly dispersed in the sponge, by cutting the sponge obtained as the drug vehicle to a suitable size, it becomes possible to make the final concentration of the drug in each cut piece (each cut piece of vehicle) fixed. Also, if the drug is oil-soluble, when the drug is blended, blending can be achieved by dissolving the drug in the organic solvent that is employed; consequently, blending of the drug can easily be performed and it can be ensured that the drug is present in a stable fashion in the form of fine particles in the sponge: this is therefore advantageous

from the point of view of drug absorption. Furthermore, as described above, since the sponge obtained in accordance with the present invention has uniform properties, when this is employed as the vehicle of an adhesive band for a drug, it has excellent adhesion and residence properties with regard to the skin or mucosa etc, and so in this respect also is very convenient for drug absorption. Furthermore, according to the present invention, when freeze-drying is performed, the polymer fibres are not likely to become aligned in a fixed direction; consequently, the inconvenience that streaks are formed in a fixed direction in the sponge is unlikely to arise.

The present invention is specifically described below with reference to practical examples.

[Practical example 1]

	Sodium carboxymethylcellulose	2.0 weight%
	Polyvinyl alcohol	1.0 "
A	Polyoxyethylene sorbitane mono-oleate [Nikkol TO-10 (manufactured by Nikko Chemicals Inc)]	2.0 "
	Purified water	75.0 "
B	1, 2-dichloroethane	20.0 "
		100.0 "

An O/W type emulsion (average particle size about 15 μ) was prepared by gradually adding 1, 2-dichloroethane (oily phase B) to an aqueous phase A obtained by dissolving sodium carboxymethylcellulose and polyvinyl alcohol Nikkol TO-10 in purified water and stirring. Next, this emulsion was frozen and was dried under vacuum in the frozen condition to evaporate the 1, 2-trichloroethane, thereby obtaining a spongiform porous film.

[Practical example 2]

	Methylcellulose	2.0 weight%
	Hydroxyethylcellulose	8.0 "
	Polyoxyethylene	2.0 "
A	hardened castor oil derivative [Nikkol HCO-60 (manufactured by Nikko Chemicals Inc)]	
	Purified water	73.0 "

B	Cyclohexane	12.0 “
	Chloroform	3.0 “
		100.0 “

An O/W type emulsion (average particle size about 30 μ) was prepared by adding a mixture of cyclohexane and chloroform (oily phase B) to an aqueous phase A obtained by dissolving methylcellulose, hydroxyethylcellulose and Nikkol HCO-60 in purified water and emulsifying by stirring. Next, this emulsion was freeze-dried to evaporate the cyclohexane and chloroform, thereby obtaining a spongiform porous film.

[Practical example 3]

	Sodium polyacrylate	3.0 weight%
	Polyvinyl alcohol	2.0 “
	Polyoxyethylene stearate	1.5 “
A	[Nikkol MYS-55 (manufactured by Nikko Chemicals Inc)]	
	Polyoxyethylene stearate [Nikkol MYS-25 (manufactured by Nikko Chemicals Inc)]	0.5 “
	Purified water	63.0 “
B	Cyclohexane	20.0 “
	Chloroform	10.0 “
		100.0 “

An O/W type emulsion (average particle size about 10 μ) was obtained in the same way as in the case of practical example 2; this was dried to obtain a spongiform porous film.

[Practical example 4]

	Hydroxyethylcellulose	8.0 weight%
	Sodium carboxyethylcellulose	1.0 “
A	Newpol PE-68 (manufactured by Sanyo Kasei Inc)	2.0 “
	Purified water	69.0 “
B	1, 2-dichloroethane	15.0 “
	Cyclohexane	5.0 “
		100.0 “

An O/W type emulsion (average particle size about 40 μ) was obtained in the same way as in the case of practical example 2; this was freeze-dried to obtain a spongiform porous film.

[Practical example 5]

A	Methylcellulose	2.5 weight%
	Sodium polyacrylate	1.5 "
	Polyoxyethylene sorbitane monolaurate [Nikkol TL-10 (manufactured by Nikko Chemicals Inc)]	1.5 "
	Polyoxyethylene sorbitane monolaurate [Nikkol TO-10 (manufactured by Nikko Chemicals Inc)]	1.0 "
	Purified water	53.5 "
B	Chloroform	10.0 "
	Cyclohexane	30.0 "
		100.0 "

An O/W type emulsion (average particle size about 30 μ) was obtained in the same way as in the case of practical example 2; this was then freeze-dried to obtain a spongiform porous film.

This spongiform film had more pores than the spongiform films of practical examples 1 to 4 and was flexible.

No residual organic solvent was detected in any of the spongiform films of the above practical examples 1 to 5.

4. Brief description of the drawings

The drawing is a perspective view showing an example of an adhesive bandage for a body cavity produced using a sponge obtained according to the present invention.

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